Remarks

Entry of the following response, as well as reconsideration and withdrawal of the rejections of record, is respectfully requested.

Arguments presented in the Amendment dated October 30, 2008, and in the Response dated June 18, 2008 are incorporated herein in their entireties.

Summary of Status of Amendment and Office Action

In the present amendment, claims 8, 15, 18, and 19 are amended, new claims 27 and 28 are added, and no claim is canceled. Therefore, claims 8-12, 15-22 and 24-28 are pending in the application.

As discussed below in the summary of the telephonic interview, claims 8, 15, 18 and 19 are amended to restore the subject matter claimed prior to the previous Amendment. New claims 27 and 28 replace claims 13 and 14 that were canceled in the previous Amendment. Accordingly, it is respectfully submitted that the claim amendments do not raise any issue of new matter.

In the non-final Office Action dated January 28, 2009, claims 8-12, 15-22 and 24-26 are rejected under 35 U.S.C. § 103 as obvious over Fahrig et al. (WO 96/23506, English Translation). Claims 8-12, 15-22 and 24-26 are also rejected under 35 U.S.C. § 112 as indefinite.

Interview Summary

Applicants thank Supervisory Examiner Jiang and Examiner Henry for the telephone interview conducted on May 14, 2009. Arnold Turk and Paul Braier represented Applicants during the interview.

Claim Amendments

As an initial matter, Applicants discussed the history of this patent application relating to the claim amendments. Specifically, it was pointed out that the final rejection dated September 19, 2008, rejected certain claims, and objected to other claims as depending from rejected claims, but otherwise recited allowable subject matter. It was pointed out that in an Amendment dated October 20, 2008, Applicants amended the claims to recite the allowable subject matter, and canceled the rejected subject matter without disclaimer, expressly reserving the right to again submit claims reciting the canceled subject matter. However, the non-final rejection dated January 28, 2009, withdrew allowability of the claims and instead rejected them again over the same art previously utilized.

As Applicants explained, because the October 20, 2008, amendments were made based on the Examiner's indication of allowability, and because that allowability was withdrawn in the non-final rejection of January 28, 2009, Applicants should be permitted to add the canceled subject matter back into the claims. The examiners agreed that this would be appropriate, and the claim amendments entered.

Obviousness Rejection

During the interview, Applicants provided reasons why the cited reference does not teach or suggest the presently claimed subject matter, and in fact teaches away from the presently claimed subject matter.

Moreover Applicants brought to the Examiners' attention that the present application presents unexpected results sufficient to overcome any asserted prima facie case of obviousness, even if established.

The examiners acknowledged Applicants' representations, and indicated that another search would be conducted to ascertain the state of art regarding administration of drugs during a recovery phase, without a cytostatic agent.

The Rejection Of Claims as Obvious Should be Reconsidered and Withdrawn

The Office Action withdrew the indication of allowability and reinstated the rejection of claims 8-12, 15-22 and 24-26 under 35 U.S.C. § 103 (a) as obvious in view of Fahrig et al. (WO 96/23506, English translation) (hereinafter, "the Fahrig PCT"). The Office Action acknowledges that the Fahrig PCT does not disclose administering a 5' substituted nucleoside (e.g., BVDU) during a recovery phase after a cytostatic chemotherapy cycle. The Office Action asserts that administering a 5' substituted nucleoside during such a recovery phase would be obvious in view of the Fahrig PCT because the document teaches that concurrent administration of BVDU and a cytostatic agent reduces the build-up of resistance to cytostatic treatment. It is the position in the rejection that since the Fahrig PCT discloses that BVDU and/or its metabolites can reduce build-up of resistance in cytostatic treatment, it would have been obvious to administer BVDU after administration of cytostatics during a recovery phase.

As pointed out during the interview, the rejection of the claims as obvious should be reconsidered and withdrawn for at least the following reasons. The Fahrig PCT does not teach or suggest the presently claimed subject matter, but in fact teaches away from the subject matter recited in Applicant's claims. Moreover, the present application makes a sufficient showing of unexpected results to overcome a prima facie case of obviousness, even if established.

The Fahrig PCT teaches away from the presently-claimed invention because the Fahrig PCT suggests a theory of action that suggests that administering a 5'-substitute nucleoside during a recovery phase would be ineffective. In particular, the Fahrig PCT teaches that 5'-substituted

nucleosides work during administration of a cytostatic by inhibiting the mechanism by which cancer cells shuttle the cytostatic out of the cell. By inhibiting this mechanism, it is suggested that the 5'-substituted nucleoside increases concentration of the cytotoxic agent, thereby leading to increased cell death (apoptosis). This teaches the person of skill in the art that administering a 5'-substituted nucleoside during a recovery phase (when there is no cytostatic present) would be ineffective, because doing so would only inhibit a mechanism that, because of the absence of cytostatic, is already non-operational.

The scientific theory presented in the Fahrig PCT does not explain or suggest why the presently claimed invention works. More to the point, because of the effect that 5'-substituted nucleosides have on inhibiting shuttling cytotoxic agents out of cancer cells, ***one of ordinary skill in the art would have expected such compounds not to have any significant effect if administered during a recovery phase after a cytostatic chemotherapy cycle.***

Therefore, the Fahrig PCT does not teach or suggest the presently claimed invention, and in fact teaches away from the present invention. The Office Action, therefore, does not establish a *prima facie* case of obviousness, and it is respectfully requested that the rejection should be withdrawn.

Even if the Office Action had established a *prima facie* case of obviousness (which Applicants maintain is not the case), the present application contains a sufficient showing of unexpected results to overcome the rejection. The Federal Circuit has stated that "unexpected results may be sufficient to rebut a *prima facie* case of obviousness." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed.Cir.2006); see also *In re De Blauwe*, 736 F.2d 699, 706 n. 8 (Fed.Cir.1984) ("A proper showing of unexpected results will rebut a prima facie case of obviousness."). "The basic principle behind this [rule] is straightforward — that which would

have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Mayne*, 104 F.3d 1339, 1343 (Fed.Cir.1997). Of special relevance to the present case, *In re Soni*, 34 USPQ2d 1684, 1687-1688, 54 F.3d 746, 750 (Fed. Cir. 1995), held that a showing of substantially improved results for invention, and a statement that results were unexpected, suffices to establish unexpected results absent evidence to the contrary.

As noted during the interview, the present application presents the surprising discovery that administration of a 5' substituted nucleoside during a recovery phase unexpectedly provides better chemotherapeutic results than where there is no such administration during the recovery phase. See Paragraph **[0014]** and **[0016] - [0019]** of the published application.

Moreover, Applicant has additional unexpected results that are included in the attachment to the Amendment that was submitted with the Response filed June 18, 2008. The unexpected results include results presented in co-pending U.S. Patent Application Ser. No. 11/853,540 (made of record in the Supplemental Information Disclosure Statement filed concurrently with this Amendment). The Examiner is invited to review Application Ser. No. 11/853,540 and/or to review the Attachment submitted in this case on June 18, 2008. If the Examiner so requires, then the Attachment can be put into the form of a Declaration under 37 C.F.R. 1. 132.

As seen in the June 18, 2008, Attachment (which in places employs the term RP101 for BVDU) tumors in rats actually grew faster when the rats were treated with BVDU in the absence of chemotherapy (Attachment, page 1, lines 6-10). Moreover, BVDU exhibited a small benefit in rats when administered only on the same day as the cytostatic agent (Attachment, page 2, lines 20-22). However, when included in a regimen including BVDU administration during the recovery phase, there was a strong anti-tumor effect (Attachment, page 3, lines 5-21).

More importantly, the unexpected beneficial effect of BVDU administered during the recovery phase is also seen in clinical (human) studies (Attachment, page 5, line 28 to page 8, line 10). In fact, in patients stricken with pancreatic cancer (one of the most virulent and lethal cancers known), ***administration of BVDU during the recovery phase in clinical studies approximately doubled the patients' survival times*** (Attachment, page 8, lines 12-13).

These results are especially surprising in view of the theory presented in the Fahrig PCT, which would not lead one of ordinary skill in the art to administer a 5-substituted nucleoside during a recovery phase.

Accordingly, the present application provides sufficient unexpected results to overcome a *prima facie* case of obviousness, had the Office Action established such a rejection (which Applicants maintain is not the case).

For at least the above reasons, the Fahrig PCT does not teach or suggest administering a 5-substituted nucleoside (e.g., BVDU) during a recovery phase after a cytostatic chemotherapy cycle. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the obviousness rejection of claims 8-12, 16 and 17.

Because the specification provides a statement and data showing substantially improved unexpected results, this case involves patentable subject matter just as *In re Soni* involved a patentable invention. Therefore, the present application provides sufficient unexpected results to overcome a *prima facie* case of obviousness. Accordingly, it is respectfully requested that the obviousness rejection be reconsidered and withdrawn.

The Rejection Of Claims under 35 U.S.C. § 112

The Office Action also rejects claims 8-12, 15-22 and 24-26 under 35 U.S.C. § 112, asserting that the phrase "a 5-substituted nucleoside comprising (E)-5-(2-bromovinyl)-2'-

deoxyuridine (BVDU)" is indefinite. Because the Amendment of October 30, 2008 canceled 5-substituted nucleoside other than (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), the Office Action asserts that it is not clear how a 5-substituted nucleoside can "comprise" (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) rather than "being" (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU).

Because the present Amendment adds back into the claims 5-substituted nucleosides other than (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), it is respectfully submitted that this rejection is moot, and should be withdrawn.

Conclusion

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention. Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested.

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully submitted,
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